REMARKS/ARGUMENTS

Claims 1-46 are pending in this application and presented for examination. Reconsideration is respectfully requested. Applicant acknowledges and appreciates the Examiner's thorough review and command of the subject matter. Nevertheless, each and every rejection is traversed for the reasons set forth below.

I. FORMALITIES

Applicant notes that the Examiner has withdrawn various claims including process claims 29-46. In this regard, it is respectfully noted that once the product claims being currently prosecuted are found allowable, commensurate process claims drawn to a method for detecting incorporation of at least one NTP into a single primer nucleic acid molecule, must be rejoined as a matter of right (MPEP § 821.04).

Applicant respectfully traverses the Examiner's "claim interpretation" section in paragraphs 5-8 of the Office Action. In this regard, the Examiner's attention is respectfully directed to MPEP § 2111. As stated therein, "claims must be given their broadest *reasonable* interpretation." [Emphasis added]. Further, as set forth in MPEP § 2111.01, "the words of a claim must be given their "plain meaning" unless such meaning is inconsistent with the specification." Further, it is improper to import claim limitations from the specification. Plain meaning refers to the *ordinary and customary* meaning given to the term by those of ordinary skill in the art.

According to the Examiner, various terms are "not defined." The Examiner then defines the terms in a manner inconsistent with their ordinary and customary meaning given to the terms by one of ordinary skill in the art. It is respectfully pointed out that the claim terms "attachment complex," "anchor," "irreversible association," and "processivity index" are to be given their ordinary and customary meaning during examination.

II. ELECTION OF SPECIES

Applicant strenuously traverses the withdrawal of claims 4-17, 20-21, 24-25, and 27-28. The foregoing claims are part of Group I, which is the elected invention. The Examiner is improperly restricting the examined claims to the elected species. The single specie was

elected for search purposes only. Once the generic claim(s) are found allowable, all of the claims drawn to species in addition to the elected species, which require all the limitations of generic claims, will also be allowable. MPEP § 806.04(d). Claims 1-3 are generic to many of the disclosed species.

In order for the Examiner to restrict between species, it is necessary to show that the species are mutually exclusive (see, MPEP § 806.04(f)). In any event, 37 CFR 1.141 provides for a reasonable number of species to be included by an allowable generic claim. As the remarks herein place the application in condition for allowance, Applicant respectfully requests that claims 4-17, 20-21, 24-25, and 27-28 be rejoined. In addition, process claims 29-46 also need to be rejoined (MPEP § 821.04).

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 1-3, 18-19, 22-23 and 26 under 35 U.S.C. § 112, first paragraph as allegedly being non-enabling. In response, Applicant respectfully traverses the rejection.

The *Wands* Analysis

As the Examiner is aware, a *Wands* analysis sets forth various factors to be considered and weighed. These factors include: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

(i) Level of skill in the art.

The Examiner states that the "the level of skill in the art is deemed to be high." Applicant is in agreement with the Examiner in that work in the field of nucleic acid sequencing and protein engineering is typically conducted at academic and commercial enterprises having scientists with advanced academic degrees and postdoctoral training in their relevant fields. Accordingly, Applicant submits that the level of skill of those in the art is very high.

(ii) Nature of the Invention.

The subject matter at issue lies in the field of nucleic acid sequencing and protein engineering. This field of art is traditionally one in which a large volume of screening, experimental design and testing is both typical and routine. Further, the claims herein embody a creative pioneering invention.

(iii) Breadth of the claims.

The Examiner characterizes the invention as follows:

> Claims 1-3, 18, 19, 22, 23 and 26 are broadly drawn to a polymerase-nucleic acid complex comprising a target nucleic acid and a nucleic acid polymerase, where the polymerase has an attachment complex comprising at least one anchor, which irreversibly associates the target nucleic acid with the polymerase to increase the processivity index.

The Examiner than states:

> ...there is no support in the specification and the prior art for the claimed invention.

Applicant respectfully agrees in-part and disagrees in-part with the Examiner's statement. Applicant agrees with the Examiner with respect to the "no support in the prior art," for the claimed invention, *i.e.*, the invention is novel and unobvious. However, the specification is replete with a teaching and disclosure of the claimed invention.

With respect to the claim scope, the Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Here, the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. With the clear guidance provided by the detailed Specification, 11 Examples and 12 Drawings, one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

(iv) Amount of Guidance Presented and (v) working examples

The specification shows no fewer than 11 Examples on how to make and use the claimed invention. Under MPEP § 2164.01(b) as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied.

In the Office Action, the Examiner states the following:

> [t]he specification provides no evidence that a complex between a nucleic acid target and a polymerase which has an anchor irreversibly associating nucleic acid with the polymerase would be both functional as a polymerase and possess increased processivity. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification (page 11, 12, [0050], [0051 Fig. 2) discloses an idea of a 9 Degrees North DNA polymerase that has two 21-amino acid sequences inserted at positions K53 and K229 of the polymerase. These two peptides are attached to the solid support. Applicant point to a structural model 1 QHT.pdb, however, this is a structural model of the 9 Degrees North DNA polymerase, not of the construct shown in Figure 2.

Applicant respectfully traverses the Examiner's characterization. In fact, Applicant submits that the specification provides clear detailed guidance accompanied with examples and drawings. For instances, Example 1 illustrates a method regarding introducing cysteine on a protein surface for attaching a fluorophore in order to assist in detecting labeled nucleotides. Example 2 illustrates engineering the addition of histidine patches to a protein

surface for attaching anchors. Example 3 illustrates the production and use of circularization of target DNA (Figures 3-5 augment the teaching of Example 3). Example 4 illustrates and teaches protein modifications of the mutant protein from Example 2, wherein a tetramethylrhodamine-5-maleimide is conjugated to position C554. Anchors such as biotin-X nitrilotriacetic acid, are added to bind to the two histidine patches. Example 5 illustrates the anchors being attached to glass cover slips. Example 7, which begins at paragraph 111, illustrates expression of a Strep-Tag II T7 DNA polymerase useful in practicing the current invention. Example 8 teaches no less than 3 methods of polymerase immobilization. For instance, Example 8 illustrates immobilization by a) surface passivation with polyethylene glycol; b) a biotinylation and streptavidin monolayer; and fused silica coverslips.

The Examiner states:

> Applicant did not show any evidence that the polymerase modified in such a way functions as a polymerase, i.e., that no major structural changes are introduced by the modifications described. Further, it is not clear how a linear DNA molecule can be possible irreversibly associated with the polymerase. In the case of a double-stranded DNA molecule, Applicant did not show that large circular molecules could be sequenced without an addition of proteins like a helicase, which relieve the torsional stress. Without such molecules present in the reaction the polymerase would need to dissociate from the DNA, thus, the processivity would not increase. Applicant also did not show that the proposed change to the polymerase structure does indeed increase processivity. Finally, in view of the fact that there are hundreds of different polymerases, both RNA-dependent and DNA-dependent, with different target specificities and structures, the guidance in the specification is insufficient to make and use the claimed invention.

In this regard, the Examiner's attention is respectfully directed to Example 9 starting at paragraph 122. This Example illustrates sequencing a cystic fibrosis mutant. A polymerase-coated coverslip is placed on the microscope and a 20 µl sample is applied under a water immersion objective lens. Data is collected and analyzed as described in Example 6 to determine whether the dUTP-TMR nucleotide is incorporated into the primer strand.

Further guidance of experimental details and teaching is shown with the setup for a residence-time detector as described in Example 10 as well as Figure 10. With reference to

Figure 10, a multicolor mixed-gas laser emits light at tunable wavelengths. The laser beam is first passed through a laser line filter and then at a right angle into a fused-silica prism which is optically connected to the fused silica flowcell by immersion oil. The labeled nucleotides flow in a buffer solution across the polymerase enzymes immobilized on the surface of the flowcell chamber. The immobilized polymerases are illuminated in the evanescent field and are imaged using a microscope with an objective lens mounted over the flowcell. Fluorescence emission at the microscope output passes through a notch filter and a long pass filter which allow the fluorescence emission to pass through while blocking scattered laser light. The fluorescence photons are focused onto a single-photon avalanche diode SPAD. Signals are processed by a constant fraction discriminator CFD, digitized by an analog-to-digital converter ADC, and stored in memory. Signal extraction algorithms are performed on the data stored in memory. These algorithms may distinguish signal from background, filter the data, and perform other signal processing functions. The signal processing may be performed off-line in a computer, or in specialized digital signal processing (DSP) chips controlled by a microprocessor. The fluorescence is recorded using, for example, a CCD camera capable of recording single fluorophore molecules. Residence times and polymerase speed may be manipulated by controlling the reaction conditions. Example 11 illustrates computer modelling to show the appearance of known (*i.e.,* simulated) incorporation events where the nucleotide is retained by a polymerase while the base-addition chemistry occurs.

Moreover, despite the Examiner's reservations, several groups have engineered processivity into polymerases. For example, by fusing binding sites for thioredoxin, or a sliding clamp to *E. coli* pol I and Taq DNA polymerase, the cognate domain binding proteins were recruited to improve processivity. For instance, it is known that the high processivity of T7 DNA polymerase is achieved through tight binding to its processivity factor, thioredoxin. (see, Bedford E. *et al.*, *Proc Natl Acad Sci U S A.* 1997 Jan 21;94(2):479-84 (abstract attached)), identified a 76-residue domain in T7 DNA polymerase responsible for this interaction. Insertion of this domain into the homologous site in *E. coli* DNA polymerase I resulted in a dramatic increase in the processivity of the chimeric DNA polymerase.

In addition, insertion of the T3 DNA polymerase thioredoxin binding domain into the thermostable Taq DNA polymerase at an analogous position in the thumb domain, converted

the Taq DNA polymerase from a low processive to a highly processive enzyme. The enhancement in processivity was 20-50-fold when compared with the wild-type Taq DNA polymerase or to the recombinant polymerase in the absence of thioredoxin. (See, Davidson *et al.*, *Nucleic Acids Res.* 2003 Aug 15;31(16):4702-9, abstract attached.)

Moreover, a protein (an archaeal proliferating cell nuclear antigen (PCNA) homologue) is known to encircle DNA as a ring in eukaryotes, tethering other proteins to DNA. The PCNA-binding domain was determined, and a hybrid DNA polymerase was constructed by grafting this domain onto the classical PCR enzyme Taq DNA polymerase. Addition of PCNA to PCR reactions catalyzed by the fusion protein greatly stimulated product generation. (See, Motz *M J Biol Chem.* 2002 May 3;277(18):16179-88, abstract attached.)

Finally, a protein engineering-based approach to significantly improve the processivity of DNA polymerases by covalently linking the polymerase domain to a sequence non-specific dsDNA binding protein has been disclosed. Using Sso7d from *Sulfolobus solfataricus* as the DNA binding protein, it was demonstrate that the processivity of both family A and family B polymerases can be significantly enhanced. (See, Wang Y., et al. *Nucleic Acids Res.* 2004 Feb 18;32(3):1197-207, abstract attached.)

As is apparent from the foregoing, the amount of guidance and the number of working examples in the specification at the very least satisifies and more likely far exceeds the enablement requirements of 35 U.S.C. § 112, first paragraph.

(vi) State of the Art (vii) Predictability in the Art

In general, the state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

Applicant acknowledges that no art is without its uncertainty. However, the clear guidance provided by the detailed Specification, 11 Examples and 12 Drawings filed with the application are ample teaching and instruction with respect to the invention now claimed. 35 U.S.C. § 112 requires the specification to be enabling only to a person "skilled in the art to which

it pertains, or with which it is most nearly connected." In this case, both the Applicant and the Examiner are in agreement with respect to "the level of skill in the art is deemed to be high."

The Examiner states that there is uncertainty with respect to polymerase structure and therefore, uncertainty exists with respect to the influence of the mutation on the polymerase functionality. The Examiner states:

> However, as can be seen from the prior art, there is a great deal of uncertainty in terms of the influence of mutations on the properties of nucleic acid polymerases, because of the way they interact with their targets....
>
> ...It is clear from the evidence presented above that it is not possible to predict *a priori* a result of structural changes introduced into a polymerase. Thus, addition of two peptides to the polymerase residues coupled with polymerase immobilization using these peptides (or other molecules), may lead to a totally inactive polymerase.

As a class of enzymes, more mutations are performed on polymerases than probably any other enzyme class. Scores of scholarly articles, journal references and texts have been written on the subject. In fact, a great deal of practical guidance is in the art on the methodologies to achieve mutation and retain activity. Given the flexibility in achieving a functional polymerase with an attachment complex, Applicant submits that many mutations can be made in any polymerase, wherein anchors are engineered and if necessary, used to immobilize the enzyme.

In addition, despite the Examiner's misgivings about the modified polymerase functioning as a polymerase, an animated model of a RB69 DNA polymerase shows that the homologous locations of the modification sites appear ridged, with little or no participation in the major conformational changes accompanying polymerization. (See, http://www.csb.yale.edu/people/wang/rb69/synthesis.qt.) Thus, the engineered polymerase-DNA complexes of the present invention are active and improve processivity.

(vii) Undue Experimentation.

As set forth in the MPEP §2164.06, "an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561

F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

The Examiner states:

> The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to make polymerase-nucleic acid complexes in which nucleic acids are irreversibly associated with the polymerase and in which the polymerase has increased processivity. The project would involve testing attachment complexes comprising anchor molecules which can be of any kind in association with the polymerase which could be either covalent or non-covalent and testing such complexes with all possible polymerases. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

However, time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Time and difficulty of experiments are not determinative if they are merely routine. Given the expert and explicit guidance of the specification, 11 Examples and 12 Drawings, coupled with the high level of skill in the art, any experiments would be merely routine.

(viii) Summary and Overall *Forman/Wands* Analysis.

As set forth in the MPEP §2164.01(a), the final step in making the determination that "undue experimentation" would have been needed to make and use the claimed invention is reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 737."

Here, both the Applicant and the Examiner are in agreement that the level of skill for one of ordinary skill in the art is very high. Given the expert and explicit guidance of the specification, 11 Examples and 12 Drawings, coupled with the high level of skill in the art, any

experiments would be merely routine. In light of the above remarks, Applicant believes that one of ordinary skill in the art can practice the invention as presently claimed according to the requirements of 35 U.S.C. §112, first paragraph. Accordingly, Applicant respectfully requests that the above rejection be reconsidered and withdrawn.

IV. REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner rejected claims 1-3, 18-19 and 26 under 35 U.S.C. § 102(b) as allegedly being anticipated by Yao *et al.*, *Genes to Cells* (1996) 1 101-113 (Yao *et al.*"). In response, Applicant respectfully traverses the rejection.

Under MPEP § 2131:

> [a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Yao *et al.* disclose a comparative study of properties of clamp loading, unloading and intrinsic stability of three naturally occurring sliding clamps. According to Yao *et al.*, the sliding clamps of chromosomal replicates are ring shaped proteins that encircle DNA and tether the replicase to the template for chain elongation. Yao *et al.* compared replicases from i) a human PCNA with those of ii) *E. Coli* and iii) T4 phage.

As explained in the Abstract of Yao *et al.*, the human PCNA clamp on DNA is a stable trimmer which slides freely and *dissociates* from DNA slowly in about 24 minutes. In other words, the PCNA claim loads and unloads and is recycled. The T4 gp45 clamp, upon finishing a template, and dissociation of the polymerase from DNA, *spontaneously dissociates* from DNA without assistance. In other words, unloads from the DNA. The clamp loaders of PCNA and β double as clamp unloaders for the purpose of clamp recycling.

Unlike the clamps of Yao *et al.*, the present claims recite a polymerase-nucleic acid complex which *irreversibly* associates the target nucleic acid with the polymerase. The complex of the present invention is not a reversible association as disclosed in Yao *et al.* There is no loading and unloading nor clamp recycling. Claim 1 sets forth:

> A polymerase-nucleic acid complex, said polymerase-nucleic acid complex comprising:
> a target nucleic acid and a nucleic acid polymerase, wherein said polymerase has an attachment complex comprising at least one anchor, which said at least one anchor *irreversibly* associates said target nucleic acid with said polymerase to increase the processivity index.

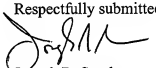
As each and every element is not found in the cited reference, the claims are not anticipated. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection.

V. CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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1: Proc Natl Acad Sci U S A. 1997 Jan 21;94(2):479-84.

The thioredoxin binding domain of bacteriophage T7 DNA polymerase confers processivity on Escherichia coli DNA polymerase I.

Bedford E, **Tabor S**, **Richardson CC**.

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Bacteriophage T7 DNA polymerase shares extensive sequence homology with Escherichia coli DNA polymerase I. However, in vivo, E. coli DNA polymerase I is involved primarily in the repair of DNA whereas T7 DNA polymerase is responsible for the replication of the viral genome. In accord with these roles, T7 DNA polymerase is highly processive while E. coli DNA polymerase I has low processivity. The high processivity of T7 DNA polymerase is achieved through tight binding to its processivity factor, E. coli thioredoxin. We have identified a unique 76-residue domain in T7 DNA polymerase responsible for this interaction. Insertion of this domain into the homologous site in E. coli DNA polymerase I results in a dramatic increase in the processivity of the chimeric DNA polymerase, a phenomenon that is dependent upon its binding to thioredoxin.

PMID: 9012809 [PubMed - indexed for MEDLINE]

1: Nucleic Acids Res. 2003 Aug 15;31(16):4702-9.

Insertion of the T3 DNA polymerase thioredoxin binding domain enhances the processivity and fidelity of Taq DNA polymerase.

Davidson JF, Fox R, Harris DD, Lyons-Abbott S, Loeb LA.

Department of Pathology, University of Washington, Seattle, WA 98195, USA.

Insertion of the T3 DNA polymerase thioredoxin binding domain (TBD) into the distantly related thermostable Taq DNA polymerase at an analogous position in the thumb domain, converts the Taq DNA polymerase from a low processive to a highly processive enzyme. Processivity is dependent on the presence of thioredoxin. The enhancement in processivity is 20-50-fold when compared with the wild-type Taq DNA polymerase or to the recombinant polymerase in the absence of thioredoxin. The recombinant Taq DNA pol/TBD is thermostable, PCR competent and able to copy repetitive deoxynucleotide sequences six to seven times more faithfully than Taq DNA polymerase and makes 2-3-fold fewer AT-->GC transition mutations.

PMID: 12907710 [PubMed - indexed for MEDLINE]

1: Nucleic Acids Res. 2004 Feb 18;32(3):1197-207. Print 2004.

A novel strategy to engineer DNA polymerases for enhanced processivity and improved performance in vitro.

Wang Y, Prosen DE, Mei L, Sullivan JC, Finney M, Vander Horn PB.

Department of Research and Development, MJ Bioworks Inc., 7000 Shoreline Court, South San Francisco, CA 94080, USA.

Mechanisms that allow replicative DNA polymerases to attain high processivity are often specific to a given polymerase and cannot be generalized to others. Here we report a protein engineering-based approach to significantly improve the processivity of DNA polymerases by covalently linking the polymerase domain to a sequence non-specific dsDNA binding protein. Using Sso7d from Sulfolobus solfataricus as the DNA binding protein, we demonstrate that the processivity of both family A and family B polymerases can be significantly enhanced. By introducing point mutations in Sso7d, we show that the dsDNA binding property of Sso7d is essential for the enhancement. We present evidence supporting two novel conclusions. First, the fusion of a heterologous dsDNA binding protein to a polymerase can increase processivity without compromising catalytic activity and enzyme stability. Second, polymerase processivity is limiting for the efficiency of PCR, such that the fusion enzymes exhibit profound advantages over unmodified enzymes in PCR applications. This technology has the potential to broadly improve the performance of nucleic acid modifying enzymes.

PMID: 14973201 [PubMed - indexed for MEDLINE]

1: J Biol Chem. 2002 May 3;277(18):16179-88. Epub 2002 Jan 22.

Elucidation of an archaeal replication protein network to generate enhanced PCR enzymes.

Motz M, Kober I, Girardot C, Loeser E, Bauer U, Albers M, Moeckel G, Minch E, Voss H, Kilger C, Koegl M.

Exploratory Research, LION Bioscience Ktiengesellschaft, D-69120 Heidelberg, Germany.

Thermostable DNA polymerases are an important tool in molecular biology. To exploit the archaeal repertoire of proteins involved in DNA replication for use in PCR, we elucidated the network of proteins implicated in this process in Archaeoglobus fulgidus. To this end, we performed extensive yeast two-hybrid screens using putative archaeal replication factors as starting points. This approach yielded a protein network involving 30 proteins potentially implicated in archaeal DNA replication including several novel factors. Based on these results, we were able to improve PCR reactions catalyzed by archaeal DNA polymerases by supplementing the reaction with predicted polymerase co-factors. In this approach we concentrated on the archaeal proliferating cell nuclear antigen (PCNA) homologue. This protein is known to encircle DNA as a ring in eukaryotes, tethering other proteins to DNA. Indeed, addition of A. fulgidus PCNA resulted in marked stimulation of PCR product generation. The PCNA-binding domain was determined, and a hybrid DNA polymerase was constructed by grafting this domain onto the classical PCR enzyme from Thermus aquaticus, Taq DNA polymerase. Addition of PCNA to PCR reactions catalyzed by the fusion protein greatly stimulated product generation, most likely by tethering the enzyme to DNA. This sliding clamp-induced increase of PCR performance implies a promising

novel micromechanical principle for the development of PCR enzymes with enhanced processivity.

PMID: 11805086 [PubMed - indexed for MEDLINE]